Measurement of 2-hydroxyglutarate in gliomas by optimized 1H-MRS at 3.0 T

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INTRODUCTION: Mutations in isocitrate dehydrogenase (IDH) 1 and 2 in the majority of WHO grade II and III gliomas and secondary glioblastomas lead to orders-of-magnitude elevation of 2-hydroxyglutarate (2HG) [1-3] and are associated with longer overall survival compared to IDH wild type tumors [4,5]. Several studies were presented at ISMRM 2011 for demonstrating the NMR feasibility of 2HG detection in gliomas *ex vivo* [6,7] and *in vivo* [8-10]. Noninvasive *in vivo* studies included short-TE PRESS [8], long-TE PRESS [9], and difference editing [10] at 3T. A 2HG molecule has five non-exchangeable J-coupled protons, giving multiplets at 2.25 (H4, H4′), ~1.9 (H3, H3′), and 4.0 (H2) ppm [11]. Reliable detection of 2HG multiplets are challenging due to their close proximity to the resonances of glutamate (Glu), glutamine (Gln), NAA, creatine (Cr), and myo-inositol [11,12]. While short-TE methods benefit from minimal T_2 signal reduction, optimized long-TE acquisition may offer improved signal selectivity. Here we report a comparison study of 2HG measurements by short- and long-TE MRS at 3T.

METHODS: A 2HG MRS study was carried out in 19 patients with gliomas using short (minimum) TE (35 ms) and long TE (97 ms) PRESS at 3T. Here, the 97 ms TE (= TE_1+TE_2 = 32+65 ms) was obtained, with numerical simulations, for maximum 2HG H4 multiplet. Written informed consent was obtained prior to the scans. Experiments were conducted in a Philips whole-body 3T scanner. A body coil was used for RF transmission and an 8-channel phased-array coil for reception. The two TEs were tested in phantoms; one with 2HG 10 mM and Cr 10 mM, and another with 2HG 6.0 mM, Glu 6.2 mM, Gln 6.2 mM, GABA 1.0 mM, Cr 4.4 mM, NAA 4.2 mM, and PC (phosphocholine) 4.2 mM. For *in vivo*, T_2w-FLAIR images were acquired to identify tumor masses. PRESS spectra were obtained, using TE = 35 and 97 ms, from a voxel positioned within the tumor. Experimental parameters included; TR = 2 s, sw = 2.5 KHz, and 2048 sampling points. The number of signal averages was 64 - 256, depending on the voxel size (4 - 8 mL). Spectra were analyzed with LCModel using basis spectra of 20 metabolites calculated using published chemical shift and J coupling constants [11,12]. Basis sets for PRESS 35 ms were created with non-selective instantaneous RF pulses (similarly to a prior study [8]), and those for PRESS 97 ms were created using the volume localization RF and gradient pulses.

RESULTS AND DISCUSSION: Due to the J coupling effects, the PRESS spectral pattern of 2HG was substantially altered from the zero-TE spectrum (**Fig. 1**). At TE = 35 ms, the H4 and H3 multiplets merged together, giving a broad composite multiplet at 1.7 - 2.4 ppm (**Fig 1a**). The 2HG signals were quite different between phantom and simulated spectra, largely due to the hard-pulse approximation in the simulation. This discrepancy between calculation and experiment disappeared when simulations were performed with the PRESS volume-localization RF and gradient pulses (data not shown). With this computer simulation, 2HG spectra at TE = 97 ms showed excellent agreement between calculation and experiment (**Fig. 1b**). The feasibility of instantaneous-RF pulse simulated and PRESS volume localized simulated spectra as basis sets was tested in composite-phantom spectra at TE = 35 and 97 ms, respectively (**Fig. 2**). The TE = 97 ms spectrum was well reproduced by the fit compared to the TE = 35 ms data, as evidenced from the residuals. Cramer-Rao lower bounds (CRLB) of 2HG, Glu, Gln and GABA were overall smaller in the 97 ms data fitting than in the 35 ms data fitting. A similar trend was observed in the fitting of *in-vivo* spectra from a tumor patient (**Fig. 3**). The 35 ms spectrum between 2.2 - 2.8 ppm was not well reproduced by the fit. The CRLB of 2HG was much larger in 35 ms data than in 97 ms data (21% *vs.* 6%). For data from 6 patients with mutated IDH (**Fig. 4**), the CRLB of 2HG was larger in the 35 ms data than in the 97 ms data in all cases. In a patient with mutated IDH (subject 4), 2HG was not measurable with infinite CRLB by the 35 ms method, whilst the 97 ms method giving a non-zero 2HG estimate with CRLB of 23%. For other 13 patients, whose IDH status was unavailable, 2HG was detectable by both methods, but CRLB was smaller in 97-ms data than in 35-ms data in all cases, despite the increased T_2 effects at 97 ms. In conclusion, the TE = 97 ms method, with properly-calculated basis sets, may allow reliable detection of 2HG compared to the short-TE method.

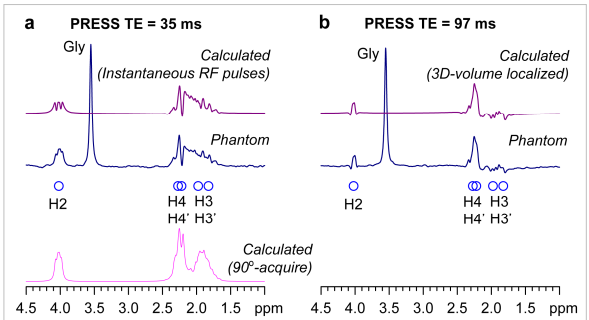

FIG 1. Calculated and phantom spectra of 2HG for PRESS TE = 35 and 97 ms at 3T. Circles depict 2HG resonances. A calculated zero-TE spectrum of 2HG is illustrated for comparison.

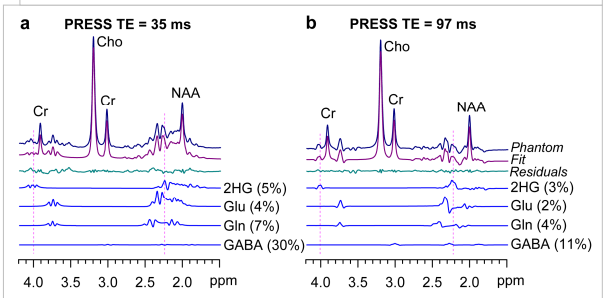

FIG 2. *In vitro* spectra from a composite phantom, obtained with PRESS TE = 35 and 97 ms at 3T, shown with fits, residuals, and spectra of 2HG, Glu, Gln and GABA. CRLB is shown in brackets.

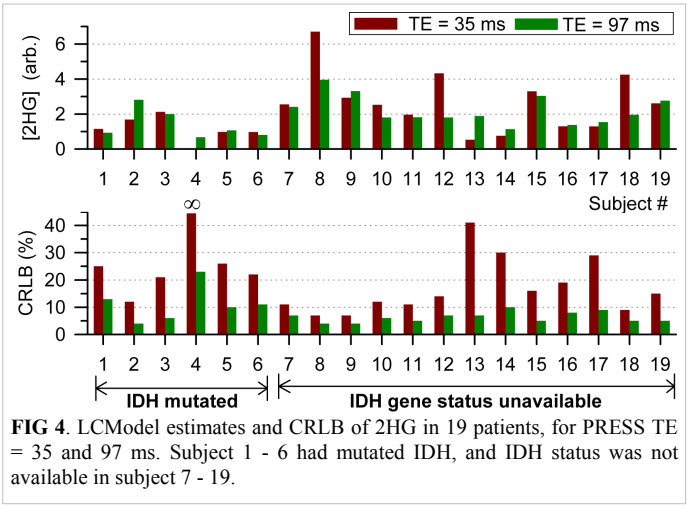

FIG 4. LCModel estimates and CRLB of 2HG in 19 patients, for PRESS TE = 35 and 97 ms. Subject 1 - 6 had mutated IDH, and IDH status was not available in subject 7 - 19.

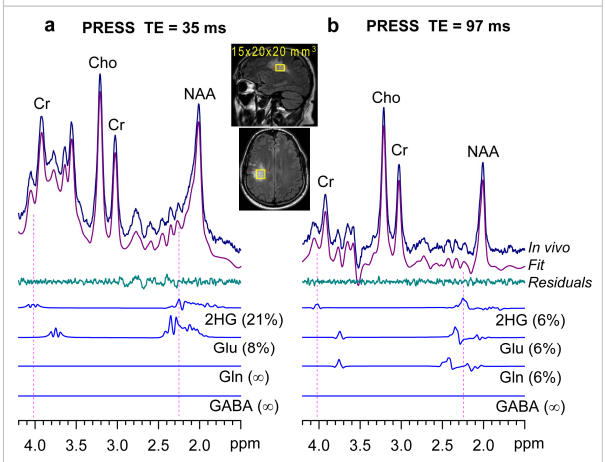

FIG 3. *In vivo* spectra from an IDH-mutated glioma patient, obtained with PRESS TE = 35 and 97 ms at 3T, are shown with fits, residuals, and spectra of 2HG, Glu, Gln and GABA (TR = 2 s; NEX = 256; voxel size 6 mL). Percentages in brackets are CRLB.

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